PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re U.S. Patent Application

Chih-Chang CHU, et al.

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For: INJECTABLE HYDROGEL MICROPSHERES FROM AQUEOUS TWO-PHASE SYSTEM

DECLARATION UNDER 37 C.F.R. 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Chih-chang Chu hereby declares:

1. I am an inventor in the above-identified patent application.

2. I have a Ph.D in polymer science from Florida State University.

3. Since 1978, I have been employed by Cornell University in the College of Human Ecology. My present title is Rebecca Q. Morgan "60 Professor of Fiber Science & Apparel Design.

4. I held visiting appointments in the Department of Dental Science at University of Liverpool in the UK, at the National Yang-Ming Medical College in Taiwan, and in the Division of Mechanics and Material Science, Center for Devices and Radiological Health at the U.S. Food and Drug Administration.

5. I serviced on the board of directors for the Society of Plastic Engineers (medical plastics division).

6. I had been on the editorial board of the Journal of Investigative Surgery.

7. Attached as Appendix A hereto is a list of selected publications where I am co-author.

8. I have considered the following patents applied in the office action of 11/24/08: Ekman et al. U.S. Patent No. 4,822,535; Jahns U.S. Patent No. 5,596,051; Mosier U.S. Patent No. 4,492,720; and Nelson U.S. Patent No. 6,596,296.

9. The product of Example 6 of Eckman differs significantly from the product produced by the process of claims of the above-identified patent application. In the product of said Example 6 dextran is a component of the microspheres wheras in claim 6 of the above-identified patent application dextrans is used as medium for microspheres formation and is not a component of the microspheres. In his Example 6, Eckman uses polyethylene glycol solution as a medium to serve as a continuous phase for microsphere formation and it does not become part of the

microsphere product. In the product obtained by the process of claim 1 of the above-identified patent application, polyethylene glycol diacrylate (different from polyethylene glycol) is in the dispersed phase and one of the components polymerized and crosslinked to become part of the microsphere product.

10. The ethylene glycol diacrylate (EGDA) disclosed by Jahns as cross-linker is disadvantageous compared to the polyethylene glycol diacrylate (PEGDA) of amended claim 1 of the above-identified patent application. When EGDA is used as crosslinker, because of its low molecular weight (compared to PEGDA), the pore size of a resulting hydrogel network is much smaller, resulting in a reduced water swelling ratio for a hydrogel microsphere which can be inappropriate for proper diffusion of larger protein macromolecules, e.g. proteins and polypeptides, out of the microsphere hydrogel network for drug delivery. Moreover PEGDA provides microspheres which are more biocompatible and more hydrophilic than does EGDA and reduces protein adsorption on a hydrogel microsphere in a physiological environment compared to EGDA. Moreover polyethylene glycol has been shown to minimize denaturing of protein and to prevent proteins from micro-climate induced instability reactions.

11. The microspheres obtained by the process of claim 4 of the above-identified patent application, i.e. the PNIPAAm/PEGDA hydrogel microspheres obtained, have at least three unique properties, thermoresponsive intelligence, swelling capability and shape for delivery by injection rather than implantation.

12. Moiser teaches that micropheres prepared in traditional organic solvents can be produced from dispersed phase droplets in the range of 50-150 microns, not microspheres prepared in aqueous solution (claim 1 of the above-identified patent application). The advantages of preparing from water solution rather in organic solvent are biocompatibility (no toxicity issue) and no denaturing of loaded proteins/peptides as occurs with organic solvents.

13. Nelson does not teach microspheres and therefore cannot teach what occurs in microspheres.

14. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date 1/15/09

Chih-Chang CHU

APPENDIX A

Selected Publications:

D. Q. Wu and **C. C. Chu**, ?Cationic poly(VCL-AETA) hydrogels and ovalbumin (OVA) release in Vitro?, J.Mater. Sci. Materials in Medicine, 19: 3593-3601, (2008).

C. C. Chu and Dajun D. Sun, ?New electrospun synthetic biodegradable poly(ester amide) drug-eluting fibrous membranes for potential wound treatment?, AATCC Symposium Proceeding ?Medical, Nonwovens, and Technical Textiles?, Oct.. 6-7, 2008, Durham, NC, pp. 60-76.

Dai Yamanouchi, Jun Wu, Andrew N. Lazar, K. Craig Kent, **C. C. Chu**, Bo Liu, ? Biodegradable arginine-based poly(ester-amide)s as non-viral gene delivery reagents?, Biomaterials, 29(22): 3269-3277, (2008).

G. M. Sun, X. Z. Zhang and **C. C. Chu**, Effect of the molecular weight of polyethylene glycol (PEG) on the properties of chitosan-PEG-poly(N-isopropylacrylamide) physical hydrogels?, J. Mater. Sci. Materials in Medicine, 19 (8):2865-2872, (2008).

Kai Guo and **C. C. Chu**, ?Copolymers of Unsaturated and Saturated Poly(ether ester amide)s: Synthesis, Characterization and Biodegradation?, J. Appl. Polym. Sci. 110 (3): 1858-1869, (2008).

D. Q. Wu and **C. C. Chu**, ?Biodegradable hydrophobic-hydrophilic hybrid hydrogels: Swelling behavior and controlled drug release?, J. Biomater. Sci. Polymer Ed 19(4): 411-429, (2008)

Kai Guo and **C. C. Chu**, ?Synthesis, characterization and biodegradation of novel poly(ether ester amide)s based on L-phenylalanine and oligoethylene glycol?, *Biomacromolecules*, 8(9): 2851-2861, (2007).

X. Z. Zhang and **C. C. Chu**, ?Influence of polyelectrolyte on the thermosensitive property of PNIPAAm-based copolymer hydrogels?, *J. Mater. Sci. Mater. in Medicine*, 18:1771-1779, (2007).

S. Namkung and **C. C. Chu**, ?Partially biodegradable temperature and pH-responsive poly (N-isopropylacrylamide)/dextran-maleic acid hydrogels: Formulation and controlled drug delivery of Doxorubicin?, *J. Biomater. Sci. Polym. Ed.* 18 (7): 901-924, (2007).

K. Guo and **C. C. Chu**, ?Biodegradation of unsaturated poly(ester-amide)s and their hydrogels?, *Biomaterials*, 28: 3284-3294, (2007).

K. Guo and **C. C. Chu**, ?Synthesis, Characterization and Biodegradation of Copolymers of Unsaturated and Saturated Poly(ester amide)s?, *J. Polym. Sci. Polym. Chem.* 45:1595-1606,

(2007).

K. Guo and **C. C. Chu**, ?Controlled release of Paclitaxel from biodegradable unsaturated poly (ester amide)s/poly(ethylene glycol) diacrylate hydrogels?, *J. Biomater Sci. Polym. Ed.* 18 (5): 489-504, (2007).

G. Jokhadze, M.Machaidze, H. Panosyan, **C. C. Chu** and R. Katsarava, ?Synthesis and Characterization of Functional Elastomeric Poly(Ester Amide) Copolymers?, J. Biomater. Sci. Polym. Ed. 18(4): 411-438 (2007).

G. M. Sun and **C. C. Chu**, "Synthesis, characterization of biodegradable dextran-allyl isocyanate-ethylamine/poly (ethylene glycol) diacrylate hydrogels and its in vitro release of albumin", *Carbohydrate Polymers*, 65: 273-287, (2006).

Sunny Namkung and **C. C. Chu**, ?Effect of Solvent Mixture on the Property of Polysaccharide-based Hydrogels Having, Temperature and pH Sensitivity ?, *J. Biomater. Sci., Polymer Ed.*, 17(5): 519 ? 546, (2006).

D. Q Wu, X. Z. Zhang, **C. C. Chu**, Functionalized 3-arm poly(e-caparolactone) maleic acid microspheres for controlled protein release?, *Am. J. Drug Delivery*, 3(4): 253-267, (2005).

X. Z. Zhang and **C. C. Chu**, ?Temperature sensitive poly(N-isopropylacrylamide)/poly (ethylene glycol) diacrylate hydrogel microspheres: formulation and controlled drug release?, *Am. J. Drug Delivery*, 3(1): 55-65, (2005)

K. Guo, **C. C. Chu**, E. Chkhaidze & R. Katsarava, ?Synthesis and Characterization of Novel Biodegradable Unsaturated Poly(Ester-Amide)s?, *J. Polym. Sci. Polym. Chem ed.*, 43:1463-1477, (2005)

Kai Guo and **C. C. Chu**, ?Synthesis, Characterization and Swelling Behaviors of Novel Biodegradable Unsaturated Poly(ester-amide)s/Poly(ethylene glycol) Diacrylate Hydrogels?, *J. Polym. Sci. Polym. Chem ed.* 43: 3932-3944, (2005)

Xian-Zheng Zhang, P. J. Lewis and **C. C. Chu**, ?Fabrication and characterization of a smart drug delivery system: Microsphere in hydrogel?, *Biomaterials*, 26(16): 3299-3309, (2005)

C. C. Chu, ?Surface degradation and microenvironmental outcomes?, IN: Surfaces and Interfaces for Biomaterials, Pankaj Vadgama, ed. Woodhead Publishing LTD, Oxford, England (2005)

X. Z. Zhang, G. M. Sun and **C. C. Chu**, ?Temperature sensitive dendrite-shaped

PNIPAAm/Dex-AI hybrid hydrogel particles: Formulation and properties?, *European Polymer Journal*, 40: 2251-2257, (2004)

X. Z. Zhang, D. Q. Wu, **C. C. Chu**, ?Synthesis and Characterization of Partially Biodegradable, Temperature and pH Sensitive Dex-MA/PNIPAAm Hydrogels?, *Biomaterials*, 25:4719-4730, (2004)